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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/545,283	04/07/2000	Bryan J. Boyle	HYS-5	1585

7590 12/13/2002

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EXAMINER
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ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/545,283	Boyle et al
Examiner	**Art Unit**
Jehanne Souaya	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 6, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *10, 11, 20, and 31* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *10, 11, 20, and 31* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Nov 6, 2002* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☑ Interview Summary (PTO-413) Paper No(s). 22
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 10, 11, 20, and 31 are currently pending in the instant application. The after final response filed 11/6/2002 has been entered. Upon further review, the examiner's basis for withdrawal of the rejections of claims 10, 11, 20, and 30-32 under 35 USC 101 and 112/enablement was found to be in error, therefore prosecution has been reopended. The rejections under 35 USC 101 and 112/enablement are set forth below. A response to applicant's arguments and declaration, filed, July 29, 2002 follow the rejections. Because applicant's canceled claims 30 and 32 in the after final amendment submitted, for the purposes of expediting prosecution as the examiner had indicated claims 10, 11, and 20 allowable, the applicant is invited to resubmit the claims for entry. It is noted that because the claims are not actually pending, the 101 and 112/first paragraph enablement rejections are set forth with regard to claims 10, 11, 20 and 31, however upon reentry of the claims, the rejections will be applied to such claims. The examiner will reiterate the rejection of claims 30 and 32 under 35 USC 112/first paragraph under Written Description as well as the response to applicants arguments filed July 29, 2002 for applicants convenience. This action is NON-FINAL.

Claim Rejections - 35 USC § 101

Definitions: [from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the

logic and facts that are offered by the applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the specific and substantial tests (see below).

"Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. ' 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility."

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a specific or substantial utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, or course, be tempered by consideration of the context and nature of the invention. For example, it a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial asserted utility would be considered to be met.

A "Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

See also the MPEP at 2107 - 2107.02.

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 10-11, 20, and 31 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

The claims are drawn to isolated polypeptides comprising the amino acid sequence of SEQ ID NOS 4 or 6, to compositions and kits comprising these polypeptides, to an isolated polypeptide comprising an amino acid which is 99% identical to the amino acid sequence of SEQ ID NO 4 or 6, and to a polypeptide encoded by a polynucleotide comprising the sequence of SEQ ID NO 3. The specification teaches that SEQ ID NO 4 is a C-type lectin receptor like polypeptide. SEQ ID NO 4 corresponds to the amino acid sequence encoded by the nucleic acid of SEQ ID NO 3. The specification teaches that SEQ ID NO 6 is the extracellular portion of SEQ ID NO 4 (see p. 4, lines 28). The specification further teaches that a predicted N-linked glycosylation site is encoded between residues 110 and 112 (Arg His Trp) of SEQ ID NO 4 (p. 4, lines 29-30). The specification, however does not teach the activity or biological function of SEQ ID NOS 3, 4, or 6. At page 4, line 28, the specification asserts that SEQ ID NO 6 is useful on its own as a soluble protein, but does not disclose what this use is, teaching only that this can be confirmed by expression in mammalian cells and sequencing of cleaved product.

The specification asserts the following uses for the polypeptides. At page 7, lines 23-29, the specification teaches that the polypeptides can be used a) to generate an antibody that specifically binds the polypeptide, b) as molecular weight markers, and c) as food supplements. The specification further asserts that the polypeptide can be used to prevent, treat, or ameliorate a medical condition (sentence bridging pages 7 and 8, and page 8 first para) which involve aberrant protein expression or biological activity. The specification asserts that the polypeptides of the invention having C-type lectin receptor activity are useful for prophylaxis or treatment of disorders or diseases caused by or involving allergic reactions, inflammation, sepsis, Alzheimer's disease or other nervous system disorders, bone development, and wound healing (p. 8, lines 26-30). At page 45, lines 5-10, the specification asserts that the polypeptides can also be used in assays to determine biological activity, to raise antibodies or to elicit an immune response, as a reagent in assays designed to quantitatively determine levels of the protein in biological fluids, and to isolate correlative receptors or ligands. The claimed polypeptides, however, are not supported by a specific asserted utility because the disclosed uses of the polypeptides are non specific uses that are applicable to polypeptides in general and not particular or specific to the polypeptide being claimed. It is noted that the specification asserts that SEQ ID NO 4 may function as a shed receptor, however the specification has not demonstrated such nor is this use specific for SEQ ID NO 4 as a number of other receptors have such a function including IL-2R, TNF-alpha receptor, EPCR (endothelial cell protein receptor) and peritoneal macrophage Fc

gamma receptor. The fact that a receptor may be shed does not make clear or apparent the function or specificity of the receptor, nor does it identify the ligand for the receptor.

Further, the claimed polypeptides are not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. For example, a polypeptide can be used to obtain an antibody. The antibody could then be used in conducting research to functionally isolate the protein. The need for such research clearly indicates that the protein and/or its function is not disclosed as to a currently available or substantial utility. A starting material that can only be used to produce a final product does not have substantial asserted utility in those instances where the final product is not supported by a specific and substantial utility. In this case, none of the antibodies that are to be produced as final products resulting from processes involving claimed polypeptides have specific and substantial utilities. The research contemplated by applicant(s) to characterize potential protein products, especially their biological activities, does not constitute a specific and substantial utility. Identifying and studying the properties of a protein itself or the mechanisms in which the protein is involved does not define a "real world" context of use. Similarly, the other listed and asserted utilities as summarized above or in the instant specification are neither substantial nor specific due to being generic in nature and applicable to a myriad of such compounds. Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility of the utility has not been assessed.

It is noted that the specification teaches that SEQ ID NO 4 has 39% identity to "mouse macrophage C-type lectin" over amino acids 18-232 of SEQ ID NO 4, 49% identity to "dendritic cell immunoreceptor" and "DDB27" (which appear to be the same protein) over amino acids 39-227 of SEQ ID NO 4, and 44% identity to "mouse C-type" over amino acids 16 to 225 of SEQ ID NO 4 (p. 4). The specification further asserts the C-type lectin receptor-like proteins of the invention belong to the same family as C-type lectin receptor, mannose-binding lectins, mammon-binding lectins, and dendritic cell immunoreceptors and therefore have similar activity to these C-type lectin receptor proteins. C-type lectin receptors, however, belong to a large family of proteins exhibiting different structures and functions, such that an analysis based solely on homology or membership in a broad family does not identify the ligand or biological activity or function of SEQ ID NO 4. Akimoto et al teach (Akimoto, Y, et al. Prog. Histochem. Cytochem. 1998, vol. 33, pp 1-92) that C-type lectins are a family of lectins that have a common type of carbohydrate recognition domain (CRD), however they perform diverse biological functions including clearance of molecules from blood circulation (hepatocyte asialoglycoprotein receptors), internalization of foreign and self derived materials, (alveolar macrophage lectin), role in humoral self defense mechanisms (collectins), cell-cell adhesion (selectins), and transmembrane signaling to cells (natural killer cell receptors) (p. 12, section 2.2). With regard to the CRD, Drickamer (Curr. Opin. Struct. Biol., 1999, vol. 9, pp 585-590) teaches that evidence in the art suggests that many protein modules containing part or all of the C-type CRD motif serve functions other than saccharide recognition, and that it is appropriate to consider this motif

a characteristic of C-type lectin-like domains to reflect their similarity to CRDs of C-type lectins without necessarily implying common function (p. 585, col. 1, para 2). Figure 3 of Akimoto et al illustrates the differences in structural organization of C-type lectins, and table 3, teaches the variety of different ligands and sugars for which different C-type lectins exhibit specificity. This wide range of sugars and ligands include galactose, N-acetylgalactoseamine (GalNAc), glucose, fucose, N-acetylglucosamine (GluNAc), mannose, sulfated polysaccharides, and IgE for example. It is further noted that the specification asserts that SEQ ID NO 4 has similar activity to different types of C-type lectin receptors, including mannose binding lectins which belong to the collectin subfamily, while the "dendritic cell immunoreceptor" and "mouse macrophage C-type lectin", which the specification teaches a certain % identity to SEQ ID NO: 4, appear to belong to the type II receptors. From the teachings of Akimoto, however, it is apparent that assignment of SEQ ID NO 4 to a particular subfamily does not make apparent the function or specificity of SEQ ID NO 4 as table 3 shows that different type II receptors have different specificities and bind different ligands. For example human H1 binds galactose and N-acetylgalactoseamine while CD23 binds IgE.

Furthermore, with regard to the alignment of SEQ ID NO 4 with "mouse macrophage C-type lectin" and "dendritic cell immunoreceptor", for example, the art does not teach the function or specificity for either receptor. Balch et al (JBC, 1998, vol. 273, pp 18656-18664) teaches that comparative sequence analysis suggests that "mouse macrophage C-type lectin" (referenced as mMCL by Balch) has carbohydrate binding capabilities, but that little can be postulated about the

ability or specificity of mMCL from its protein sequence alone because even within a relatively small, conserved domain, binding specificity can be altered with the mutation of only one or two amino acids (see Iobst and Drickamer, JBC, 1994, vol. 269, pp 15512-15519). Balch further teaches that some molecules containing C-type lectin domains have been shown to bind peptide sequences such that this versatility makes predicting putative ligands for this type of lectin domain difficult, and that for mMCL this task is even more challenging because a serine rather than the typically conserved proline separates the two critical sugar binding residues corresponding to Glu-185 and Asn-187 (p. 18662, paragraph bridging col. 1 and 2). Bates et al (J. Immunol., 1999, vol. 162, pp 1973-1983) teach that dendritic cell immunoreceptor (DCIR) is a type II membrane glycoprotein (abstract) and that it is of potential importance in regulation of dendritic cell function, however it's function or activity in such regulation is not taught. Bates teaches that the Ca^{2+} ligating residues are well conserved in DCIR, displaying closest homology with hepatic ASG-PR, but that localization of the gene on chromosome 17 could suggest that DCIR represents an evolutionary intermediate between the NK cell receptors and the hepatic lectins [different type II lectins - see Akimoto et al] and that the cytoplasmic domain of DCIR contains one ITIM motif which is present in the cytoplasmic tail of C-type lectin like molecules expressed by NK cells (p. 1979, col. 2, last two sentences of last full para; and bridging para pp 1979-1980). A sequence search of SEQ ID NO 4 revealed 43.5 % identity to dectin 2, a C-type lectin, however studies showed that a his-dectin 2 fusion protein failed to exhibit specific binding to mannose, fucose, lactose, GluNAc or GalNAc (Ariizumi et al, JBC, 2000, vol. 275, pp 11957-

11963; p. 11960, col. 2, last full para.). Therefore the indicated % identity and similarity to C-type lectin receptors would not indicate to one of skill a specific or substantial utility for the claimed polypeptides. While it is credible that SEQ ID NO 4 belongs to the C-type lectin receptor family, the prediction of putative domains does not provide the artisan with a "real world" use for the claimed polypeptides. The specification does not teach what the biological activity or function of SEQ ID NO 4 is, nor does it demonstrate which diseases it is associated with or would be used to treat. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecules and therefore lacks support regarding utility. Further experimentation would be required of the skilled artisan to determine a use for the polypeptides of the claimed invention. As noted by Brenner v. Manson, 383 US 519, 535-536 (1996), "Congress intended that no patents be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use - testing... a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

Claim Rejections - 35 USC § 112

Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-11, 20, and 31 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The teachings in the specification are set forth above (section 13). Given that the art teaches the unpredictability of determining function and specificity with regard to C-type lectins based on homology analysis, and that the specification does not teach the activity or function of the claimed molecules, the skilled artisan would have to perform trial and error to determine the function and activity of the claimed molecules, the results of which are unpredictable, thus constituting undue experimentation.

Response to Arguments

The examiner withdrew the rejections under 35 USC 101 and 112/first paragraph enablement in the previous office action with regard to applicants comments (in the response filed July 29, 2002 as well as the Declaration under 37 CFR 1.132) on the teaching of 99% identity of SEQ ID NO 4 and BDCA-2. The basis for this withdrawal, however, was found to be in error because the specification did not teach homology of SEQ ID NO 4 to BDCA-2, nor that BDCA-2 was a plasmacytoid dendritic cell specific antigen. Such points are explained in further detail below. The response and the declaration teach that BDCA2 has homology to plasmacytoid dendritic cell specific antigen-2 (BDCA-2), a type II C-type lectin (p. 9, 2nd full para of response

as well as section 9 of the Declaration). The response and the declaration teach that analysis of BDCA-2 mRNA expression by PCR showed that BDCA-2 is selectively expressed in plasmacytoid dendritic cells and that similar to other C-type lectin receptors, BDCA-2 also was shown to exhibit antigen uptake as demonstrated by studies using Ag-mAb complexes, and induced a rapid and transient rise in intracellular calcium, consistent with the role in antigen capture and calcium mediated signal transduction pathway. This evidence has been thoroughly reviewed but was not found persuasive for the following reasons. Firstly, the examiner could not find any teaching in the specification as to homology between SEQ ID NO 4 and BDCA-2. Secondly, the evidence with regard to expression and antigen uptake, role in antigen capture, and calcium mediated signal transduction pathway, noted above with regard to BDCA-2, also does not find support in the specification at the time the application was filed. Further, as stated in applicants response, such expression and antigen uptake is similar to other C-type lectin receptors, however neither the response nor the declaration teach what C-type lectin receptors these are, thus it is unclear whether this activity is specific with regard to SEQ ID NO 4, BDCA-2, or C-type lectin receptors. As stated in the rejection above, C-type lectin receptors, although share similar domains, such domains do not impart the same specificity, activity, or biological function such that the function of any C-type lectin receptor is immediately apparent based on it's structure. Applicant's are directed to the definitions of utility, presented above. The response and the declaration assert that the activity of C-type lectin receptors including BDCA-2 and homologous proteins such as SEQ ID NO 4 to mediate antigen capture and modulate

inflammatory mediators, specifically IFN a/b is a specific utility inasmuch as it is not a utility shared by all polypeptides. This argument has been thoroughly reviewed but was not found persuasive. Firstly, the teaching of the activity of C-type lectin receptors, BDCA-2, and SEQ ID NO 4 with regard to IFN a/b is not supported by the specification at the time of filing. Further, although mediation of antigen capture and modulation of inflammatory mediators is not specific to polypeptides in general, it is not specific to SEQ ID NO 4, but to a class of proteins, C-type lectin receptors, which is a class composed of proteins with different functions and specificities such that membership alone to the broad class does not make the specific function or specificity of any single C-lectin receptor immediately apparent to one of skill in the art. Further, the specification does not teach what inflammatory mediators are modulated by the claimed SEQ ID NOs nor what antigen capture is mediated by SEQ ID NO 4. Absent such teaching, the specification does not teach a specific function that takes advantage of the specific properties of SEQ ID NO 4, and not C-type lectins in general. The response and the declaration teach that systemic erythromatosus (SLE), an inflammatory disease, is characterized by increased levels of IFN a/b, which play a role in the pathogenic mechanism of SLE, and that administration of anti-BDCA-2 mAb to SLE patients provides another therapy for inhibiting IFN a/b production by PDC's. This argument has been thoroughly reviewed but was found unpersuasive because the specification does not teach or demonstrate that administration of anti-BDCA-2 or SEQ ID NO 4 mAb to SLE patients provides therapy for inhibiting IFN a/b production by PDC's. The response further traverses that the specification teaches the use of C-type lectin receptors polypeptides for

the management and or treatment of inflammatory disorders. This argument as well as the sections in the specification at 5.8.7, 5.8.15, and 5.8.18 have been thoroughly reviewed but were found unpersuasive to overcome the rejection because the specification does not teach any single inflammatory disorder, but instead suggests that the polypeptides of the present invention can be used to elicit an immune response or for prophylaxis or treatment of disorders or diseases such as allergic reactions, inflammation, autoimmune disorders, such that the claimed polypeptides are not supported by a specific utility because such disclosed uses are not specific for any single disease or specific or particular to SEQ ID NO 4, or C-lectin receptors. Further, the specification does not teach any specific function or activity of the claimed polypeptides with regard to such treatment or elicitation of an immune response, therefore the skilled artisan would be required to perform further experimentation to establish which disease it could be used to treat, or whether it was capable of eliciting an immune response.

The remainder of the section in applicants response and the declaration will be addressed, in order, below. The response (p. 4) and the declaration assert that, as disclosed in the specification, SEQ ID NO 4 exhibits homology to members of the C-type lectin receptor family. The examiner does not question this assertion, nor that SEQ ID NO 4 contains domains, such as a carbohydrate recognition domain and a Ca2+ binding domain, that indicate that it is a member of the C-type lectin family of proteins. The examiner, however, did indicate that the C-type lectin receptors belong to a large family of proteins exhibiting different functions, such that an analysis based on homology or membership to a broad family does not identify the ligand or

biological activity or function of SEQ ID NO 4. As stated in the rejection above, the specification asserts that SEQ ID NO 4 has similar activity to different types of C-type lectin receptors, including mannose binding lectins which belong to the collectin subfamily, while the "dendritic cell immunoreceptor" and "mouse macrophage C-type lectin", which the specification teaches a certain % identity to SEQ ID NO: 4, appear to belong to the type II receptors. From the teachings of Akimoto, however, it is apparent that assignment of SEQ ID NO 4 to a particular subfamily does not make apparent the function or specificity of SEQ ID NO 4 as table 3 shows that different type II receptors have different specificities and bind different ligands. For example human H1 binds galactose and N-acetylgalactoseamine while CD23 binds IgE. Furthermore, with regard to the alignment of SEQ ID NO 4 with "mouse macrophage C-type lectin" and "dendritic cell immunoreceptor", for example, the art does not teach the function or specificity for either receptor. Balch et al (JBC, 1998, vol. 273, pp 18656-18664) teaches that comparative sequence analysis suggests that "mouse macrophage C-type lectin" (referenced as mMCL by Balch) has carbohydrate binding capabilities, but that little can be postulated about the ability or specificity of mMCL from its protein sequence alone because even within a relatively small, conserved domain, binding specificity can be altered with the mutation of only one or two amino acids (see Iobst and Drickamer, JBC, 1994, vol. 269, pp 15512-15519). Bates et al (J. Immunol., 1999, vol. 162, pp 1973-1983) teach that dendritic cell immunoreceptor (DCIR) is a type II membrane glycoprotein (abstract) and that it is of potential importance in regulation of dendritic cell function, however it's function or activity in such regulation is not taught. Bates

teaches that the Ca2+ ligating residues are well conserved in DCIR, displaying closest homology with hepatic ASG-PR, but that localization of the gene on chromosome 17 could suggest that DCIR represents an evolutionary intermediate between the NK cell receptors and the hepatic lectins [different type II lectins - see Akimoto et al] and that the cytoplasmic domain of DCIR contains one ITIM motif which is present in the cytoplasmic tail of C-type lectin like molecules expressed by NK cells (p. 1979, col. 2, last two sentences of last full para; and bridging para pp 1979-1980). Thus, from such teaching, it can be seen that C-lectin receptors have different specificities, and that specific functions or activities of some of them are unknown, demonstrating that membership to the C-lectin receptor family does not impart a function or activity that is immediately apparent to one of skill in the art to the claimed polypeptide. With regard to the teaching of SEQ ID NO 4 exhibiting 99% identity to BDCA-2, such teaching is not supported by the specification at the time of filing.

The response (p.5) and exhibit 2 teach a sequence alignment of SEQ ID NO 4 with BDCA-2, DCIR and C-type lectin 6, and further teach a C-lectin domain and a C-type consensus sequence within the domain are conserved. This alignment has been thoroughly reviewed, and while the examiner agrees that the proteins in question, as well as other C-type lectins share conserved domains, this conserved domain does not impart a specific function or activity that takes advantage of the specific properties of SEQ ID NO 4. The response further asserts that an EPN motif, at amino acids 172-174 indicate a mannose or glucose binding specificity, which is similar to BDCA2 and mouse macrophage receptor. This argument has been thoroughly

reviewed but was found unpersuasive to overcome the rejection. Firstly, as stated above, a teaching of BDCA-2 having a mannose or glucose binding specificity does not find support in the specification. Secondly, while this motif is similar to mouse macrophage receptor, the specification does not teach the function of mouse macrophage receptor nor does the specification teach or characterize the mannose binding motif in SEQ ID NO 4. Further, the specification teaches homology of SEQ ID NO 4 to DCIR, but teaches that DCIR has a variant amino acid motif (EPS) which confers binding specificity for galactose. This teaching is a further illustration that C type lectins, although sharing conserved domains and regions, exhibit different specificity. While the response and the declaration demonstrate that SEQ ID NO 4 and BDCA-2 share common C-lectin domains, such comparison does not find support in the specification. Further, applicants references to BDCA-2 are in a WO patent (WO 01/36487) and a reference (Dzionek, 2001) both published after the filing date of the instant invention, thus any common domains between BDCA-2 and SEQ ID NO 4 do not appear to be well known or implied at the time the application was filed.

The response and the declaration submit eMATRIX and Pfam Analyses for SEQ ID NO 4 that are consistent with C-type lectin receptor polypeptides. This evidence has been thoroughly reviewed, however, such evidence was not in question. The specification supports that SEQ ID NO 4 is a member of C-type lectin family of proteins through BLAST searches and identification of domains, such as the CRD domain. Further, the rejections outlined above were not made based on a questioning of such evidence. Rather, the rejections are set forth with regard to the

fact that membership in this broad class of proteins does not impart a specific activity or function to the polypeptide of SEQ ID NO 4, such that a specific or substantial utility is immediately apparent to one of skill in the art. For example, with regard to the CRD, Drickamer (Curr. Opin. Struct. Biol., 1999, vol. 9, pp 585-590) teaches that evidence in the art suggests that many protein modules containing part or all of the C-type CRD motif serve functions other than saccharide recognition, and that it is appropriate to consider this motif a characteristic of C-type lectin-like domains to reflect their similarity to CRDs of C-type lectins without necessarily implying common function (p. 585, col. 1, para 2). The specification provides evidence that SEQ ID NO 4 is homologous to 4 different C-type lectin polypeptides, however as stated previously, the specification does not teach the function of these C type lectin proteins such that no common specific function or activity was immediately apparent to the skilled artisan. Armed with the knowledge presented in the specification, the skilled artisan would have to perform further experimentation to determine a specific and substantial utility for the claimed polypeptides. This is exemplified by the teachings in the declaration with regard to the expression of SEQ ID NO 4 mRNA in resting CD4+ and CD19+ cells, but not activated CD4+ cells and activated CD19+ cells. This expression was not taught in the specification, nor would an artisan, reading the specification, determine, without experimentation, that the expression pattern of SEQ ID NO 4 mRNA was that as presented in the declaration. Further, Dzionek et al (The Journal of Immunology, vol. 165, 2000, pp 6037-6046), which was also published after the filing date of the specification, teaches that different BDCA's, BDCA-2, BDCA-3, and BDCA-4 are expressed in

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different dendritic cell populations. The specification, however, does not teach or indicate such specificity of either SEQ ID NO 4 or BDCA-2. This is evidence, that further experimentation would be required by the skilled artisan to determine specificity or function of SEQ ID NO 4. The response and the declaration assert that the expression of SEQ ID NO 4 suggest a role in lymphocyte activation and/or differentiation similar to another type II C-type lectin receptor CD23, however this argument was not found persuasive because the specification does demonstrate such activity or compare the expression of SEQ ID NO 4 to CD23 nor does the specification teach why such would be considered a substantial utility. Further, while the response and the declaration teach that DCIR was shown to be expressed on myeloid CD14+ cells, such evidence was published after the filing date of the specification (Figdor et al, 2002) and such specific expression for DCIR was not readily apparent at the time the application was filed, based on the teachings in the specification. Further, where such evidence supported in the specification, it is unclear as to why such would be considered a substantial utility.

The response and the declaration teach that members of the C-type lectin receptor serve as antigen receptors and regulate migration of dendritic cells and their interactions with lymphocytes (Figdor, et al 2002). This argument was not found persuasive to impart a specific utility or substantial to SEQ ID NO 4 because the teaching that C-type lectin receptors serve as antigen receptors is a general teaching that does not indicate what specific antigen is bound to distinct C-type lectin receptors nor how or why the skilled artisan would use a C-lectin receptor to regulate migration of dendritic cells and their interactions with lymphocytes, for example.

Further, neither the declaration nor the response teach how C-type lectins regulate migration of dendritic cells and their interactions with lymphocytes such that the skilled artisan might be able to establish a predictable correlation between the structure of SEQ ID NO 4 and the structure of C-lectins responsible for this activity. It is further noted, as stated in the paragraph above, that the Figdor et al reference was published after the filing date of the instant specification. The response and the declaration assert that members of the C-lectin receptors can be used in a screen for immune-related disorders and the management and/or treatment of immune related disorders. This argument has been thoroughly reviewed but was not found persuasive to impart a specific utility to the claimed polypeptides because 1) such a teaching is not made with regard to SEQ ID NO 4, but C-type lectin receptors in general, and 2) the specification does not demonstrate any immune specific disorders, generally or specifically, that can be screened using SEQ ID NO 4. While the response asserts that this is a real world use because members of the C-type lectin receptor family are useful for screening immune related disorders, the specification does not demonstrate such use, nor does it demonstrate any specific immune related disorders that are "screened" with C-type lectin receptors. Additionally, it is unclear how a C-type lectin "screens" for immune related disorders. For example, does such refer to specific C-type lectin receptors as markers for a specific immune related disorder? The response's reference to anti BDCA-2 antibodies, or their potential usefulness in treating systemic lupus erythromatosus is neither demonstrated nor supported by the specification. Further, with regard to therapies utilizing antibodies to C-type lectin polypeptides to correct or ameliorate defects in the processes

mediated by antigen recognition and immune cell interactions, such is not considered specific or substantial because the specification does not teach or demonstrate any specific "defects", "process", "antigens", or "immune cell interactions" with C-lectin receptor polypeptides in general or the claimed polypeptides specifically nor the use of any specific C-type lectin polypeptide or claimed polypeptides with specific management or treatment or a specific inflammatory disease.

The response and the declaration teach that SEQ ID NO 4 mRNA expression was detected in peripheral blood, mononuclear cells, tonsil, spleen, peripheral blood leukocytes, fetal spleen, placenta, lung and testis, however this evidence was not found persuasive to overcome the rejections because such expression does not impart any specific or substantial utility for SEQ ID NO 4. it is unclear, from this teaching, what specific or substantial utility is readily apparent from a polypeptide that is expressed in such a myriad of different tissues (placenta, testis, tonsil, lung, peripheral blood). While the specification states at page 43, lines 6-10 that C-type lectin receptors are involved in inflammatory diseases such as asthma, the specification does not teach how or which C-type lectins are involved with asthma such that the skilled artisan could establish a predictable correlation between the structure of SEQ ID NO 4 and the structure of C-type lectins and the uncharacterized "involvement" of C-type lectins with asthma. Further this statement does not teach how this "involvement" with asthma would establish a readily apparent function or use for SEQ ID NO 4. Further, although C-type lectin receptors may be expressed in immune cells and tissues, it is unclear, nor does the specification teach, how such are "involved

in immune related reactions" such that a skilled artisan would find a readily apparent use for SEQ ID NO 4 with regard to inflammation and asthma. For example, it is unclear if SEQ ID NO 4 is a marker for inflammation or asthma, or can be used to treat inflammation or asthma, or how it would be used to treat inflammation or asthma. The specification does not make such clear. The response and the declaration traverse the examiner's position that "the fact that a receptor may be shed does not make clear or apparent the function or specificity of the receptor, nor does it identify the ligand for the receptor". The response teaches that another member of the C-type lectin class, L-selectin, was shown to be shed as a result of activation of leukocytes and that L selectin is a calcium dependent C-type lectin known to mediate the rolling and tethering of leukocytes on endothelial surfaces, and in particular mediates the homing of naïve lymphocytes and plays a role in the recruitment of leukocytes to inflammatory sites. The response also teaches that CD23, is shed and the soluble portion has immune activity. This argument has been thoroughly reviewed but was found unpersuasive. The examiner's statement was made with regard to the teachings in the specification. Given that the specification teaches only homology of SEQ ID NO 4 to different C-type lectin receptors, whose function are not taught, some of which are in different families of C-type lectin, and teaches that SEQ ID NO 4 may function as a shed receptor, such teaching, absent further experimentation, does not make the specificity or biological activity of SEQ ID NO 4 readily apparent. CD23 and L-selectin belong to different families of C-type lectins. Further, it is not unclear how the teaching that L selectin mediates the rolling and tethering of leukocytes on endothelial surfaces and that the soluble portion of CD23

has immune activity make a common function or activity between the two proteins apparent such that a common activity or function between them and SEQ ID NO 4 is also apparent. The declaration provides evidence that SEQ ID NO 4 was shown to be secreted or cleaved from the cell surface, however, such evidence was not persuasive to overcome the rejection because the examiner did not question the fact that SEQ ID NO 4 could be shed.

In summary, the response states that consistent with the teachings of the specification, the utilities known by those of ordinary skill in the art, and the data presented in the declaration, that is clear that the polypeptides of the present invention can be used as prognostic and diagnostic markers for the presence of immune related disorders or diseased states. This argument has been thoroughly reviewed but was found unpersuasive for the reasons made of record above. Further, the specification does not demonstrate any prognostic or diagnostic use for SEQ ID NO 4 and any specific immune related disorder or diseases state associated with asthma, inflammation and infection. Further, the argument is not found persuasive because the specification contemplates the use of SEQ ID NO 4 in treating such "non specific" immune related disorders or disease states, but does not teach or demonstrate how, nor does the specification teach how SEQ ID NO 4 is both a marker for and can be used to treat any general or specific immune related disorder or disease state associated with asthma, inflammation and infection. The skilled artisan would have to perform further extensive experimentation to establish if and how SEQ ID NO 4 can be used as such.

The rejection under 35 USC 112, first paragraph with regard to written description, made in the office action of 10/22/2002, of previously pending claims 30 and 32 is reiterated below.

Written Description

Claim 30 and newly added claim 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following rejection contains grounds maintained from the previous office action with regard to claim 30 and newly applied with regard to newly added claim 32.

With regard to claim 30 and newly added claim 32, the claims are drawn to a polypeptide sequence which is 99% identical or 90% identical, respectively, to the amino acid of SEQ ID NO 4 or SEQ ID NO 6. Such a recitation encompasses mutants of SEQ ID NO 4 or 6 as well as variants of SEQ ID NOS 4 or 6 without altered function. The specification, however, does not teach what the function or activity of SEQ ID NO 4 or 6, nor does the specification teach which amino acids can be altered such that the function of SEQ ID NO 4 or 6 are altered, or remain intact. The specification only teaches that SEQ ID NO 4 possesses sequence identity to a few C-type lectin like receptors and asserts the C-type lectin receptor-like proteins of the invention belong to the same family as C-type lectin receptor, mannose-binding lectins, mammon-binding lectins, and dendritic cell immunoreceptors and therefore have similar activity to these C-type lectin receptor proteins. C-type lectin receptors, however, belong to a large family of proteins

exhibiting different structures and functions, such that an analysis based solely on homology or membership in a broad family does not identify the ligand or biological activity or function of SEQ ID NO 4. Balch et al (JBC, 1998, vol. 273, pp 18656-18664) teaches that comparative sequence analysis suggests that "mouse macrophage C-type lectin" (referenced as mMCL by Balch, and which possesses 39% amino acid identity to SEQ ID NO 4) has carbohydrate binding capabilities, but that little can be postulated about the ability or specificity of mMCL from its protein sequence alone because even within a relatively small, conserved domain, binding specificity can be altered with the mutation of only one or two amino acids (see Iobst and Drickamer, JBC, 1994, vol. 269, pp 15512-15519). Balch further teaches that some molecules containing C-type lectin domains have been shown to bind peptide sequences such that this versatility makes predicting putative ligands for this type of lectin domain difficult. Therefore, since the specificity, biological activity or function of SEQ ID NOS 4 or 6 have not been taught, and the art clearly teaches that homology analysis alone does not make clear the function of a C-type lectin receptor, the recitation of 99% identity encompasses mutants and variants that have not been described by the specification. Further, the recitation of 90% identity further encompasses homologs and allelic variants from any source, that have not been described by the specification. The recitation of the amino acid sequences of SEQ ID NOS 4 and 6 is not representative of the functionally different proteins from this broad class, nor do the teachings in the specification make clear to the skilled artisan which amino acids can be changed to result in either a protein with similar or altered activity to the polypeptides of SEQ ID NOS 4 or 6.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of polypeptides comprising the sequence of SEQ ID NOS: 4 or 6 or a polypeptide encoded by a polynucleotide comprising the sequence of SEQ ID NO 3, the skilled artisan cannot envision the detailed chemical structure of the encompassed proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making or isolating it. The polypeptide itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary

skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

Accordingly, the specification does not provide a written description of the invention of claim 30 and newly added claim 32.

Response to Arguments

The response traverses the rejection. The response traverses that the production of a number of species that are encompassed within the claimed genus is described throughout the specification, for example, at page 34, line 25, to page 36, line 29. This argument has been thoroughly reviewed but was not found persuasive because the specification does not teach the sequences of such species nor does the specification teach which amino acids can be altered with or without altering the activity or function of the protein of SEQ ID NO 4. As stated above, with the exception of polypeptides comprising the sequence of SEQ ID NOS: 4 or 6 or a polypeptide encoded by a polynucleotide comprising the sequence of SEQ ID NO 3, the skilled artisan cannot envision the detailed chemical structure of the encompassed proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making or isolating it. The polypeptide itself is required.

The response further traverses that applicants have not relied solely on analysis based solely on homology or membership in a broad family, but provide herewith data from PCR

studies of mRNA expression and Western Blot analysis to confirm the function or activity shared in common with other members of the C-type lectin receptor family, and more specifically the type II member, BDCA-2. This argument has been thoroughly, but was found persuasive only in part. The written description rejection has been withdrawn with respect to the points raised in the previous office action with regard to whether SEQ ID NO 4 is a full length protein because exhibit 4 asserts that SEQ ID NO 4 is a full length ORF. However, the response was not found persuasive as to a sufficient number of species of the claimed genus being taught by the specification. Furthermore, the references cited above exemplify the difficulty of altering a single amino acid in a C-lectin receptor protein. Balch et al (JBC, 1998, vol. 273, pp 18656-18664) teaches that comparative sequence analysis suggests that "mouse macrophage C-type lectin" (referenced as mMCL by Balch, and which possesses 39% amino acid identity to SEQ ID NO 4) has carbohydrate binding capabilities, but that little can be postulated about the ability or specificity of mMCL from its protein sequence alone because even within a relatively small, conserved domain, binding specificity can be altered with the mutation of only one or two amino acids (see Iobst and Drickamer, JBC, 1994, vol. 269, pp 15512-15519). Although SEQ ID NO 4 exhibits 99% identity to BDCA-2, neither the specification nor the art teach which amino acids in either SEQ ID NO 4 or BDCA-2 can be altered or deleted such that the skilled artisan could envision what the detailed chemical structure of a variant or homolog of SEQ ID NO 4 with altered or maintained function or activity would look like. For these reasons and the reasons made of record above and in previous office action, the rejection is maintained.

Conclusion

5. Pending claims 10, 11, 20, and 31 are rejected.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Art Unit 1634
Jehanne Souaya
12/6/02